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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 16

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ABSTRACT

Objective: We present prenatal diagnosis and molecular cytogenetic characterization of a small supernumerary marker chromosome (sSMC) derived from chromosome 16.

Case report: A 28-year-old woman underwent amniocentesis at 17 weeks of gestation because of abnormal maternal serum screening for Down syndrome. Amniocentesis revealed a karyotype of 47,XY,+mar[5]/46,XY[9]. Parental karyotypes were normal. Prenatal ultrasound findings were unremarkable. Array comparative genomic hybridization (aCGH) analysis of cultured amniocytes revealed a *de novo* 16% gene dosage increase of 16q11.2-q22.1. Repeat amniocentesis at 21 weeks of gestation revealed a karyotype of 47,XY,+mar[10]/46,XY[31]. aCGH analysis of uncultured amniocytes revealed a result of arr 16q11.2q22.1 (46,492,626–68,867,969) × 2.20 with a log2 ratio of 0.15 encompassing *RPGRIP1L*, *FTO*, *SLC6A2*, *BBS2* and *CDH1*. Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes detected partial trisomy 16q in 36/137 (26.3%) of uncultured amniocytes. Polymorphic DNA marker analysis on amniocytes and parental bloods excluded uniparental disomy 16. Premature labor occurred at 25 weeks of gestation, and a 585-g male baby without craniofacial dysmorphism was delivered and survived. At age 1½ years, pediatric follow-ups revealed normal psychomotor development, normal body weight, short stature, congenital hypothyroidism, hearing impairment and hypospadias in the neonate, and the peripheral blood had a karyotype of 46,XY in 40 cultured lymphocytes.

Conclusion: aCGH, interphase FISH and polymorphic DNA marker analyses of uncultured amniocytes are useful for confirmation of prenatally detected mosaic sSMCs at amniocentesis.

Introduction

A small supernumerary marker chromosome (sSMC) is an extra structurally abnormal chromosome that cannot be identified by conventional cytogenetics and has a size equal to or smaller than that of chromosome 20 [1]. With the advent of molecular cytogenetic technology, prenatal diagnosis of an sSMC(16) has been well described [2–28]. Here, we present an additional case with mosaic sSMC(16) and a 22.4-Mb partial duplication of 16q11.2-q22.1 presenting normal psychomotor development, normal body weight, short stature, congenital hypothyroidism, hearing impairment and hypospadias at age 1½ years during postnatal follow-ups.

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Case report

A 28-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of abnormal second-trimester maternal serum screening for Down syndrome with a Down syndrome risk of 1/53 calculated from the levels of 2.8 multiples of the median (MoM) of α-fetoprotein (AFP), 12.9 MoM of β-human chorionic gonadotropin (β-hCG), 0.76 MoM of unconjugated estriol (uE3) and 7.93 MoM of inhibin A in the maternal serum at 17 weeks of gestation. Amniocentesis revealed a karyotype of 47,XY,+mar[5]/46,XY[9]. Among 14 colonies of cultured amniocytes, five colonies had a karyotype of 47,XY,+mar, whereas nine colonies had a karyotype of 46,XY. The parental karyotypes were normal, and prenatal ultrasound findings were unremarkable. Array comparative genomic hybridization (aCGH) analysis of cultured amniocytes revealed a *de novo* 16% gene dosage increase of 16q11.2-q22.1. The marker chromosome was likely an sSMC(16). The parents requested a repeat amniocentesis at 21 weeks of gestation. Repeat amniocentesis revealed a karyotype of 47,XY,+mar[10]/46,XY[31]. Among 41 colonies of cultured amniocytes, 10 colonies had a karyotype of 47,XY,+mar (Fig. 1), whereas 31 colonies had a karyotype of 46,XY. Simultaneous aCGH analysis of uncultured amniocytes using Roche ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA) revealed a result of arr 16q11.2q22.1 (46,492,626–68,867,969) × 2.20 with a log2 ratio of 0.15 and a 22.37-Mb gene dosage increase encompassing the Online Mendelian Inheritance in Man (OMIM) genes of *RPGRIP1L*, *FTO*, *SLC6A2*, *BBS2* and *CDH1* (Fig. 2). Interphase fluorescence *in situ* hybridization (FISH) analysis using the bacterial artificial chromosome probes of RP11-775B19 (16q21) and RP11-1011D21 (16q12.2) on uncultured amniocytes detected partial trisomy 16q in 36/137 (26.3%) of uncultured amniocytes comparing with 1–4% (1–4/108) in normal controls (Fig. 3). Polymorphic DNA marker analysis of DNAs extracted from amniocytes and parental bloods using polymorphic DNA markers excluded uniparental disomy 16. Premature labor occurred at 25 weeks of gestation, and a 585-g male baby without craniofacial dysmorphism was delivered and survived. At the age of 1½ years, pediatric follow-ups revealed a normal psychomotor development, a normal body weight, short stature, congenital hypothyroidism, hearing impairment and hypospadias in the neonate, and conventional cytogenetic analysis of peripheral blood revealed a karyotype of 46,XY in 40 cultured lymphocytes. No seizures occurred during infancy.

Discussion

The present case had a low-level mosaicism for an sSMC(16) with partial duplication of 16q11.2-q22.1 and mild clinical abnormalities of congenital hypothyroidism, short stature and hypospadias at the follow-ups at 1½ years of age. The short stature in the neonate is likely caused by hypothyroidism. Congenital hypothyroidism has not been reported to be associated with trisomy 16q11.2-q22.1, and congenital hypothyroidism is not related to specific chromosome abnormalities [29]. Ballif et al. [30] reported hypothyroidism in a 13-year-old male with unrecognized microdeletion syndrome of 16q11.2-q12.2. However, Uccellatore et al. [29] suggested that the association of hypothyroidism with chromosomal variants is only a chance concurrence. On the other hand, hypospadias have been noted in cases of trisomy 16 mosaicism [31,32] and duplication of 16q (16q23.1→qter) [33].

Clinical reports with a proximal-intermediate duplication are rare, and all were associated with phenotypic abnormalities [34–36]. Gustavasson et al. [34] reported a 7-year-old girl with a duplication of 16q12.1-q22.1 and phenotypic findings of a lumbosacral myelomeningocele, an Arnold-Chiari II malformation, seizures, severe mental retardation, visual impairment, strabismus, facial dysmorphism and developmental delay. Lonardo et al. [35] reported a 5-year-and-7-month-old girl with a duplication of 16q11.2-q22.1 and phenotypic findings of postural, motor and speech delay, severe learning difficulties, behavioral problems, obesity, microcephaly and facial dysmorphism. Odak et al. [36]

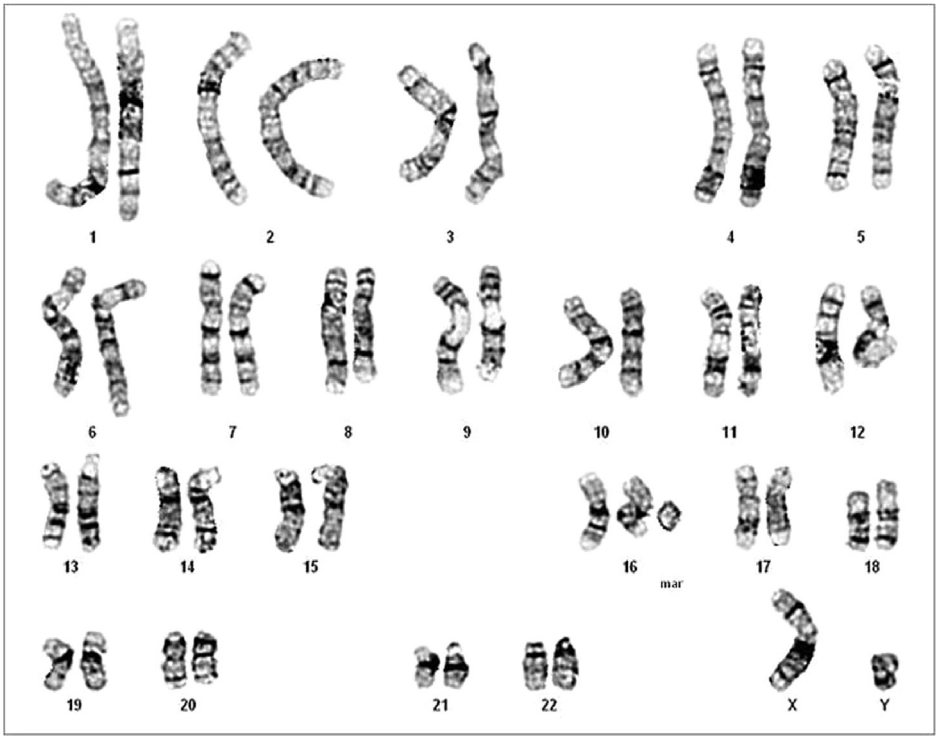

Fig. 1. A karyotype of 47,XY,+mar. mar = marker chromosome.

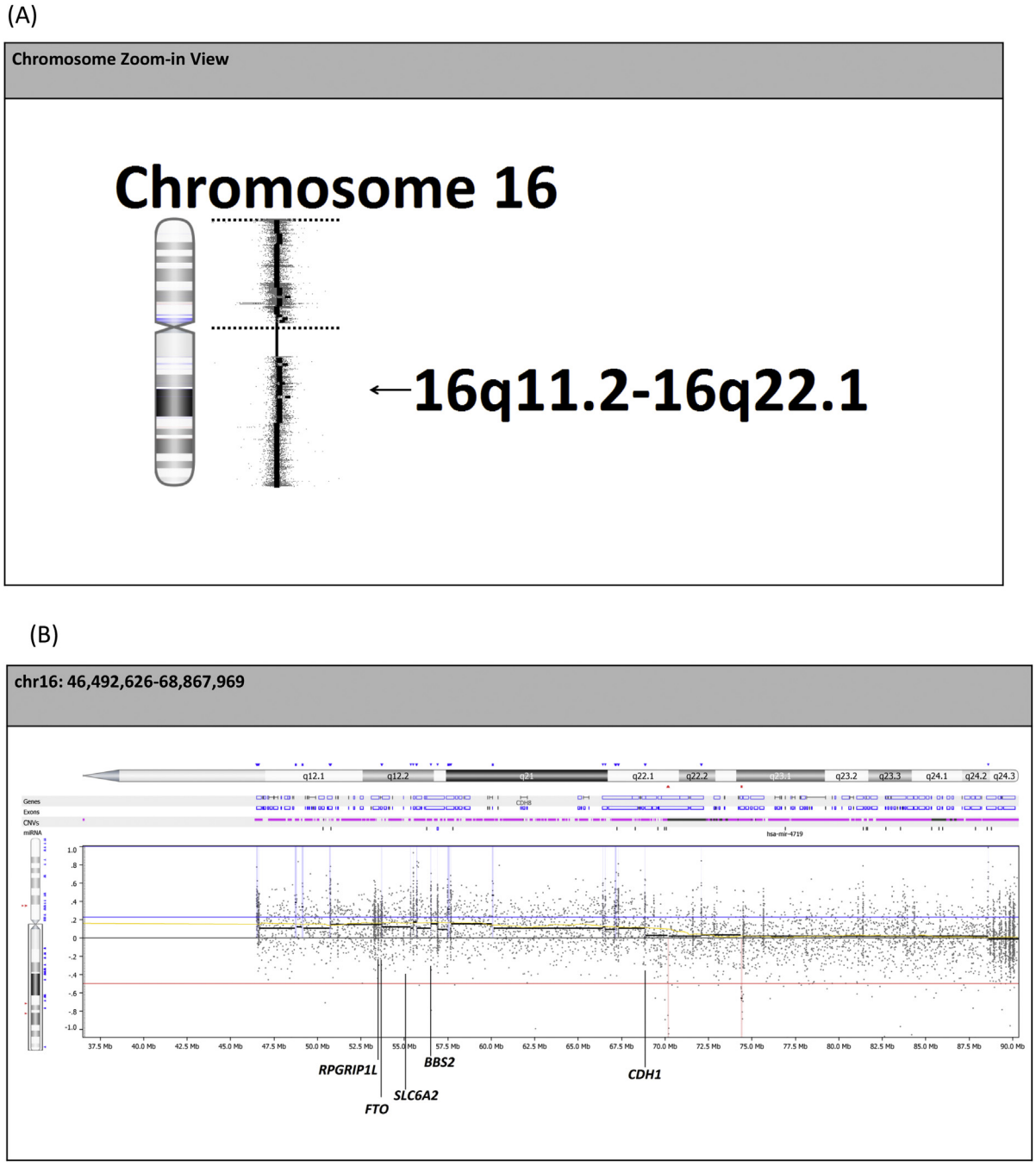

Fig. 2. Array comparative genomic hybridization on uncultured amniocytes shows a result of arr 16q11.2q22.1 (46,492,626–68,867,969) × 2.20 with a log2 ratio of 0.15 and a 22.37-Mb gene dosage increase encompassing the OMIM genes of *PRGRIP1L*, *FTO*, *SLC6A2*, *BBS2* and *CDH1*. (A) and (B) chromosome 16 zoom-in views.

reported a 10-year-old girl with a duplication of 16q12.1-q21 and phenotypic findings of speech delay, learning difficulties, aggressive behavior and dysmorphic facial features.

The present case had a 22.37-Mb duplication of 16q11.2-q22.1 encompassing the genes of *RPGRIP1L*, *FTO*, *SLC6A2*, *BBS2* and *CDH1*. Mental retardation, obesity, facial dysmorphism and digital abnormalities have been proposed to be associated with 16q proximal duplication [35,37,38]. *RPGRIP1L* (OMIM 610937; 16q12.2) is a ciliogenesis gene that is associated with autosomal recessive ciliary disorder of COACH syndrome (OMIM 216360), Joubert syndrome type 7 (OMIM 611560) and Meckel syndrome type 5 (OMIM 611561). *FTO* (OMIM 610966; 16q12.2) is a fat mass- and obesity-associated gene that is associated with autosomal recessive growth retardation, developmental delay and facial dysmorphism (OMIM 612938), and obesity susceptibility (OMIM 612460). *FTO* polymorphism has been observed to be associated with type 2 diabetes [39]. *SLC6A2* (OMIM 163970; 16q12.2) encodes norepinephrine transporter which is a regulator of norepinephrine homeostasis and is associated with orthostatic intolerance (OMIM 604715). *BBS2* (OMIM 606151; 16q12.2) is a ciliogenesis gene that is associated with autosomal recessive ciliary disorder of Bardet-Biedl syndrome type 2 (OMIM 615981) and retinitis pigmentosa type 74 (OMIM 616562). *CDH1* (OMIM 192090; 16q22.1) encodes cadhedrin and is associated with multiple cancers such as endometrial, gastric, ovarian, breast and prostate cancers.

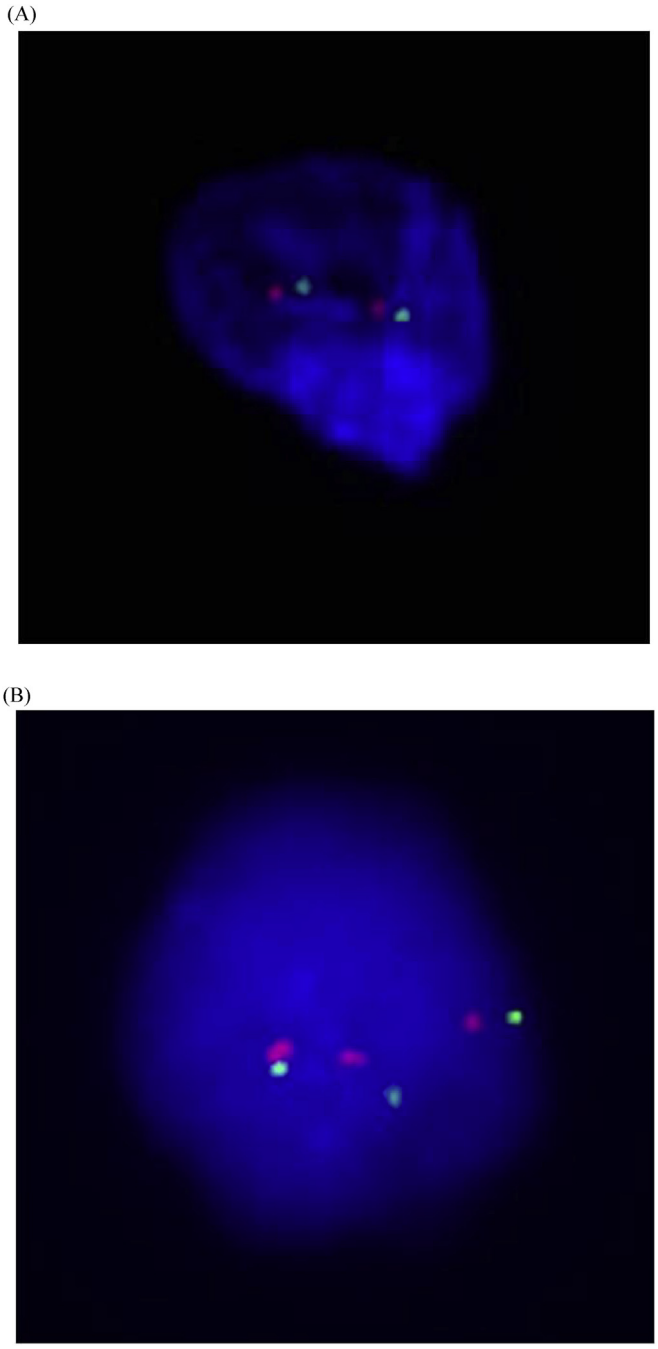

Fig. 3. Interphase fluorescence *in situ* hybridization analysis using the bacterial artificial chromosome probes of RP11-775B19 [16q21; 58,714,669–58,895,465; fluorescein isothiocyanate (FITC), spectrum green] and RP11-1011D21 (16q12.2; 53,600,093–53,802,738; Texas Red, spectrum red) shows (A) a normal disomy 16 cell with two green signals and two red signals, and (B) a cell with an sSMC(16) with three green signals and three red signals. sSMC = small supernumerary marker chromosome.

In summary, we present prenatal diagnosis and molecular cytogenetic characterization of an sSMC(16) with postnatal follow-ups. Our case demonstrates that aCGH, interphase FISH and polymorphic DNA marker analysis of uncultured amniocytes are useful for confirmation of prenatally detected mosaic sSMCs at amniocentesis.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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